

---

# (12) UK Patent Application (19) GB (11) 2 054 588 A

---

(21) Application No 8022612

(22) Date of filing  
10 Jul 1980

(30) Priority data

(31) 7917986

(32) 11 Jul 1979

(33) France (FR)

(43) Application published  
18 Feb 1981

(51) INT CL<sup>3</sup> C07C 91/02  
A61K 31/13 31/44  
C07D 213/04

(52) Domestic classification  
C2C 1530 215 220 226  
227 22Y 246 250 251  
25Y 29X 29Y 30Y 313  
31Y 322 323 32Y 332  
338 364 36Y 500 50Y  
620 621 624 634 644  
650 652 661 662 672  
682 699 802 80Y AA LF  
LJ LW

(56) Documents cited  
GB 1178400

GB 1141606

(58) Field of search  
C2C

(71) Applicant

Societe Industrielle de  
Produits de Synthese  
Rue de Beaucaire  
49240 Avrillé  
France

(72) Inventors

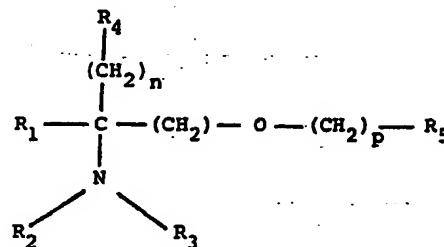
Déran Robert Torossian  
Claude Paul Joseph  
Roux  
Gilbert Gustave Aubard

(74) Agents

Frank B Dehn & Co  
Imperial House  
15/19 Kingsway  
London  
WC2B 6UZ

(54) Amino-ether oxides and pharmaceutical formulations thereof

(57) Amino-ether oxides of formula:



in which R<sub>1</sub> is lower alkyl, R<sub>2</sub> and R<sub>3</sub> which are the same or different are hydrogen or lower alkyl, R<sub>4</sub> is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen or lower alkoxy, R<sub>5</sub> is a phenyl radical op-

tionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical, n is zero, 1 or 2, m and q are 0 or 1 and p is an integer from 0 to 9, have local analgesic, spasmolytic and anaesthetic activity.

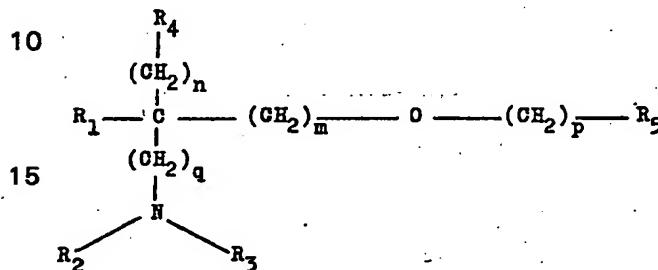
GB 2 054 588 A

## SPECIFICATION

## Amino-ether oxides and the preparation and pharmaceutical formulation thereby

5 The present invention relates to novel amino-ether oxides, a process for the preparation thereof and use thereof in human and veterinary medicine. 5

The amino-ether oxides according to the invention conform to the formula:



20 in which: 20

R<sub>1</sub> is a lower alkyl,

R<sub>2</sub> and R<sub>3</sub> which are the same or different are hydrogen or lower alkyl,

R<sub>4</sub> is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents

25 which are identical or different, halogen or lower alkoxy,

R<sub>5</sub> is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical,

n is equal to zero, 1 or 2,

30 m and q are, independently of one another, equal to zero or to 1,

p is an integer ranging from 0 to 9.

By lower radical are meant radicals having from 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, especially 1 to 4 carbon atoms in a straight or branched chain.

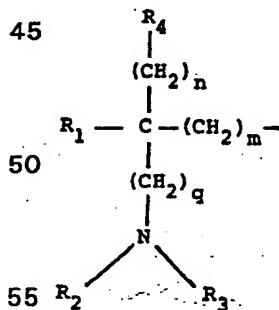
35 If R<sub>5</sub> is alkyl, it is preferably methyl. If the amino-ether oxides are halogenated, they are preferably brominated or chlorinated. 35

The invention also embraces the acid addition salts of amino-ether oxides, notably those of mineral acids, such as halohydrates, sulphates, phosphates, or organic acids such as maleates, citrates, malates, tartrates, methanesulphonates, camphosulphonates, benzoates, etc.

The invention covers both racemic and optically active forms which can be separated,

40 particularly by forming salts with optically active acids. 40

To prepare the amino-ether oxides according to the invention, a compound of formula AX can be condensed with an alcoholate of formula BOM, one of A and B being the radical



55 when the other is the radical R<sub>5</sub>-(CH<sub>2</sub>)<sub>p</sub>-, X being an anionic radical and M being an alkali metal, the acid addition salts being obtained conventionally by salification by means of the selected acid.

60 X preferably represents bromine or chlorine, but it can also be an anionic sulphate, benzosulphonate, methanesulphonate or p-toluenesulphonate radical.

The alcoholates in which the radicals R<sub>1</sub> to R<sub>4</sub> appear can be prepared by reacting an alkali metal M, especially sodium or potassium or their hydrides or amides, with the corresponding amino-alcohols prepared as described in French Patent Nos. 912,577 or 71,08700 or 65 according to the method described by Chapman and Triggle in "J. Chem. Soc." 1963, page

10

15

20

25

30

35

40

45

50

55

60

65

4835. The reaction is effected in aromatic solvents such as benzene, toluene, xylenes or in ether solvents such as diethyl ether, dioxane, tetrahydrofuran or aprotic solvents such as dimethyl sulphoxide, dimethyl formamide (DMF), acetonitrile, dimethyl acetamide, hexamethyl phosphorotriamide (HMPT); this last group of solvents is especially preferred when the salification agent is 5 in the form of the hydride or amide of the alkali metal M. 5

The reaction is effected at a temperature of between 0 and 140°C, especially between 20 and 110°C.

The reaction time varies according to the reagents and the temperature and is between 15 minutes and 24 hours, especially between 30 minutes and 6 hours.

10 The reactive esters and particularly the halides in which the radical  $R_5$  appears are prepared according to the method of Shepard and Noth described in the "Journal of the American Chemical Society" 1950, page 4364, in which alcohol is reacted with thionyl chloride, or according to the method of Ctvrtnik described in "Chemical Abstracts" 1956, Vol. 50 10130 c, by chloromethylation of aromatic nuclei. The halides and others in which the radicals  $R_1$  to  $R_4$  appear are prepared, for example, according to the method described in "Organic Syntheses" Coll. Vol. IV, page 333, or by the numerous other methods referred to in this article. 15

These latter methods generally make it possible to obtain a product which can be used in the following condensation reaction:

—either as such by releasing in situ the reactive ester from its salt by the action of a strong 20 base such as an amine, for example triethylamine, or any other product which can effect this displacement; 20

—or by displacing in a previous stage the amino-alcohol ester from its salt by the action of a suitable alkaline agent such as sodium hydroxide, extraction of the liberated product by means of an organic solvent such as, for example, diethyl ether or chloroform, then evaporation of this 25 extraction solvent which leads to the reactive amino-alcohol ester which is used as such or in solution in the solvent suitable for the following condensation reaction. 25

The condensation of AX and of BOM is effected at a temperature of between 0 and 140°C, preferably between 70 and 110°C. The reaction time is between 1 and 24 hours, preferably between 4 and 12 hours. The progress of the reaction can be followed by thin-layer 30 chromatography. 30

The amino-ether oxide is separated from the reaction medium by methods well known to a person skilled in the art, such as, for example, extraction, precipitation, fractional distillation, crystallisation of salts, etc.

The following Examples illustrate the invention. 35

35 *Example 1 (preferred)*

1-[(3,4-dimethoxy)benzyloxymethyl]-1-phenyl-N,N-dimethyl-n-propylamine

$R_1$  = ethyl,  $R_2$  =  $R_3$  = methyl,  $R_4$  = phenyl,  $R_5$  = 3,4-dimethoxyphenyl,  $n = q = 0$ ,  $m = p = 1$ .

39.3 grams of sodium (1.71 mol) are introduced into 300 grams of 2-phenyl-2-dimethylamino-1-butanol (1.55 mol) in solution in 3 litres of anhydrous dioxane. 40

The mixture is refluxed with vigorous stirring to disperse the sodium.

After 6 hours 434 grams of 3,4-dimethoxy- $\alpha$ -chlorotoluene (2.34 mol) in solution in 1 litre of anhydrous dioxane are introduced within 30 minutes; the mixture is maintained for 6 hours at the reflux temperature of the solvent.

45 The suspension is filtered and the solvent to the filtrate is eliminated by distillation in vacuo. The residue is taken up with 2 litres of hydrochloric acid (2N) and extracted with diethyl ether. The ether phases are removed and the aqueous acid phase is made alkaline in the cold with sodium hydroxide solution (10N) in a quantity sufficient to obtain a pH value of 12.

The oil formed is extracted with ether, the ether phases are washed with water and then dried 50 over sodium sulphate and the ether is eliminated by distillation.

The oily residue obtained is purified by fractionation in vacuo.

B.p.<sub>0.2/0.5</sub> = 187–193°C, weight: 271 grams, yield≈50%.

The DL camphosulphonate of the product is prepared in ethanol and recrystallised in ethyl acetate. Yield = 85%, M.p. = 108°C. 55

*Example 2 (preferred)*

1-[(3,4,5-trimethoxy)benzyloxymethyl]-1-phenyl-N,N-dimethyl-n-propylamine

$R_1$  = ethyl,  $R_2$  =  $R_3$  = methyl,  $R_4$  = phenyl,  $R_5$  = 3,4,5-trimethoxyphenyl,  $n = q = 0$ ,  $m = p = 1$ .

2.07 kg of oily suspension of sodium hydride at 60% (51.75 mol) in 11.6 litres of anhydrous 60 dimethylformamide (DMF) are introduced into a suitable reactor.

With stirring and maintaining the reaction temperature below 40°C about 10.00 kg of 2-phenyl-2-dimethylamino-1-butanol (51.70 mol) in solution in 8.7 litres of anhydrous DMF are introduced within 45 minutes.

After introduction the suspension is maintained for 45 minutes at about 40°C. 11.20 kg 65 (51.70 mol) of 3,4,5-trimethoxy- $\alpha$ -chlorotoluene in solution in 8.7 litres of anhydrous DMF are 65

subsequently introduced within about 35 minutes and without exceeding 60°C.

The mixture is subsequently maintained for 5 hours at 70 to 75°C and is then cooled to 20°C.

5 The suspension obtained is introduced into 250 litres of iced water and is then acidified with concentrated hydrochloric acid until a pH value of 1 is obtained.

The mixture is extracted with toluene. The toluene phases are removed and the aqueous acid phase is made alkaline until a pH value of 12 is obtained with a sodium hydroxide solution (10N) and the mixture is extracted with methylene chloride. The methylene chloride phases are washed with water, dried over  $\text{Na}_2\text{SO}_4$  and the methylene chloride is eliminated by distillation.

10 The residue is solubilised in 200 litres of hexane at boiling point, filtered hot and the filtrate cooled with stirring. 10

After the start of crystallisation the suspension is left overnight at 10°C.

The product is filtered, washed with cold hexane and dried in vacuo at ambient temperature. Weight = 12.2 kg, yield = 63%, M.p. = 55–56°C.

15 The hemi-maleate of the product is prepared and recrystallised in water. 15  
Yield = 90%, M.p. = 123–124°C.

*Example 3 (preferred)*

1-Benzylloxymethyl-1-phenyl-N,N-dimethyl-n-propylamine.

20  $R_1 = \text{ethyl}$ ,  $R_2 = R_3 = \text{methyl}$ ,  $R_4 = R_5 = \text{phenyl}$ ,  $n = q = 0$ ,  $m = p = 1$ . 20  
4.0 grams of sodium hydride at 90% (0.15 mol) are introduced into 30.0 ml of hexamethyl phosphorotriamide (HMPT).

A solution of 29.0 grams (0.15 mol) of 2-phenyl-2-dimethylamino-1-butanol in 30 ml of HMPT is introduced with stirring over about 30 minutes and without exceeding 30°C.

25 Stirring is maintained for 30 minutes after introduction and 19.0 grams of  $\alpha$ -chlorotoluene (0.15 mol) in solution in 30 ml of HMPT are then added over 30 minutes at a temperature below 40°C. 25

The suspension is then maintained with stirring for 5 hours at 70 to 75°C and is then left overnight at ambient temperature.

30 The reaction medium is precipitated in 1 litre of iced water and the mixture is acidified with hydrochloric acid in a quantity sufficient to obtain a pH value of 1 and is extracted with diethyl ether. The ether phases are eliminated and the aqueous acid phase is made alkaline by a sodium hydroxide solution until a pH value of 12 is obtained. 30

The suspension is extracted with diethyl ether, the combined ether phases are washed with 35 water and dried over anhydrous sodium sulphate and the ether is then eliminated by distillation. 35  
The residue is purified by fractional distillation in vacuo.

B.p.<sub>0.25</sub> = 157–158°C, weight = 21 grams, yield = 49.4%.

The maleate of the product is prepared in ethanol and recrystallised in water.

Yield = 95%, m.p. = 113–114°C.

40 According to the process described in Example 3, the amino-ether oxides listed in table 1 below are obtained from 2-phenyl-2-dimethylamino-1-butanol and halides of formula  $R_6-(\text{CH}_2)_pX$ . 40

TABLE 1

Example No	p	X	R <sub>5</sub>	YIELD	Characteristics
4	3	Br	—CH <sub>3</sub>	30 %	Bp 1,2 = 118-119°C
5	9	Br	—CH <sub>3</sub>	18 %	Bp 0,1 = 170-175°C
6	1	Cl		72 %	Bp <sub>0,6</sub> = 161-172°C
7	0	Cl		46 %	Bp <sub>0,6</sub> = 135-140°C
8	0	Cl		53 %	Bp <sub>0,5</sub> = 150-152°C
9	1	Cl		66 %	Bp <sub>0,6</sub> = 135-145°C
10	1	Cl		52 %	Bp <sub>0,8</sub> = 162-163°C

**Example 11**

2-[(3,4,5-trimethoxy)benzyloxy]-2-phenyl-N,N-dimethyl-n-butylamine

45 R<sub>1</sub> = ethyl, R<sub>2</sub> = R<sub>3</sub> = methyl, R<sub>4</sub> = phenyl, R<sub>5</sub> = 3,4,5-trimethoxyphenyl, n = m = 0, p = q = 1. 45Prepared according to the process described in Example 3 from 1-phenyl-1-dimethylaminomethyl-1-propanol and from 3,4,5-trimethoxy- $\alpha$ -chlorotoluene.

Yield = 70.5%, m.p. = 84-85°C.

Hydrochloride m.p. = 208-209°C.

50

50

**Example 12 (preferred)**

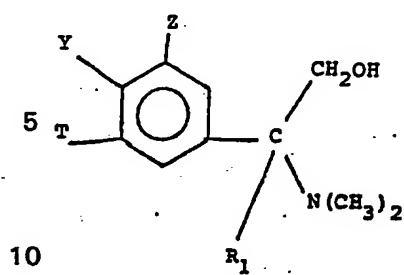
1-[(3,4,5-trimethoxy)benzyloxymethyl]-1-phenyl-N-methyl-n-propylamine

R<sub>1</sub> = ethyl, R<sub>2</sub> = H, R<sub>3</sub> = methyl, R<sub>4</sub> = phenyl, R<sub>5</sub> = trimethoxyphenyl, n = q = 0, m = p = 1.

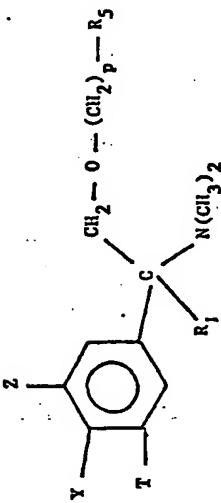
Prepared by the process of Example 3 from 2-phenyl-2-methylamino-1-butanol and from

55 3,4,5-trimethoxy- $\alpha$ -chlorotoluene; the product is obtained in the form of a colourless and viscous oil which is analytically pure and appropriate.Yield = 60%, n<sub>D</sub><sup>20</sup> = 1.5491.

The corresponding amino-ether oxides and/or their salts listed in table 2 are obtained according to the process described in Example 3 and from amino-alcohols of structure



and from halides  $\text{R}_5-(\text{CH}_2)_p-\text{X}$ .

StructuresTABLE 2

Example No	R <sub>1</sub>	P	X	R <sub>5</sub>	Z	Y	T	Yield	Characteristics
13 Preferred compound	CH <sub>3</sub>	I	Cl		H	OCH <sub>3</sub>	H	35 %	Maleate Mp = 102-105°C
14	CH <sub>3</sub>	I	Cl		OCH <sub>3</sub>	OCH <sub>3</sub>	80 %	DL camphosulfonate Mp = 80°C	
15	CH <sub>3</sub>	I	Cl		Cl	Cl	H	70 %	DL camphosulfonate Mp = 154°C
16	C <sub>2</sub> H <sub>5</sub>	I	Cl		OCH <sub>3</sub>	OCH <sub>3</sub>	H	33 %	DL camphosulfonate Mp = 120°C

**Example 17**

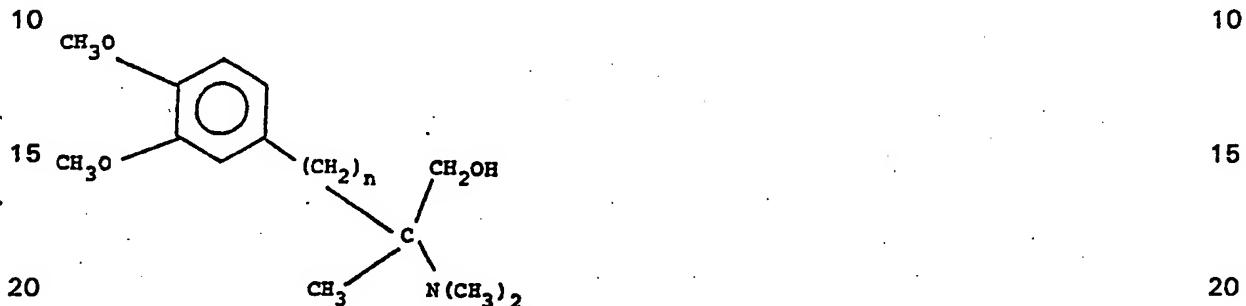
1-Benzylloxymethyl-1-methyl-(3,4-dimethoxy)-phenethylamine

 $R_1 = \text{methyl}$ ,  $R_2 = R_3 = \text{H}$ ,  $R_4 = 3,4\text{-dimethoxyphenyl}$ ,  $R_5 = \text{phenyl}$ ,  $m = n = p = 1$ ,  $q = 0$ .

Using the process described in Example 3 and starting from 2-[(3,4-dimethoxy)benzyl]-2-amino-1-propanol and from benzyl chloride the product is obtained which is crystallised in hexane.

Yield = 47%, m.p. 97–101°C.

According to the process described in Example 3 with amino-alcohols of structure



$R_1 = R_2 = R_3 = \text{methyl}$ ,  $R_4 = 3,4\text{-dimethoxyphenyl}$ ,  $q = 0$ ,  $m = 1$ , and the halides  $R_5-(CH_2)_p-X$ , the following amino-ether oxides are obtained.

Example No	n	X	p	$R_5$	Yield	Characteristics
18	1	Cl	1		62 %	Maleate $M_p = 155-157^\circ\text{C}$
19	2	Cl	1		47 %	Base $n_D^{20} = 1.5405$

**Example 20**45 1-[(2-methoxy-5-nitro)benzyloxymethyl]-1-[(4-chlorophenoxy)methyl]-N,N-dimethylethylamine  
 $R_1 = R_2 = R_3 = \text{methyl}$ ,  $R_4 = (4\text{-chlorophenoxy})$ ,  $R_5 = 2\text{-methoxy-5-nitrophenyl}$ ,  $n = m = p = 1$ ,  $q = 0$ .Prepared according to the process of Example 3, starting from 3-[(4-chlorophenoxy)-2-dimethylamino-2-methyl-1-propanol and from 2-methoxy-5-nitro- $\alpha$ -chlorotoluene.50 Yield = 10%,  $n_D^{20} = 1.5585$ .**Examples 21 and 22**

21: 1-[(4-methoxy)phenoxy]methyl-1-phenyl-N,N-dimethyl-n-propylamine.

 $R_1 = \text{ethyl}$ ,  $R_2 = R_3 = \text{methyl}$ ,  $R_4 = \text{phenyl}$ ,  $R_5 = 4\text{-methoxyphenyl}$ ,  $n = p = q = 0$ ,  $m = 1$ .55 22: 2-[(4-methoxy)phenoxy]-2-phenyl-N,N-dimethyl-n-butylamine.  
 $R_1 = \text{ethyl}$ ,  $R_2 = R_3 = \text{methyl}$ ,  $R_4 = \text{phenyl}$ ,  $R_5 = 4\text{-methoxyphenyl}$ ,  $m = n = p = 0$ ,  $q = 1$ .

100.0 grams of 4-methoxyphenol (0.80 mol) are dissolved in 1 litre of methanol. 250 ml of a methanolic solution of sodium methylate (0.80 mol) are then added with stirring and stirring is continued for 1 hour 30 minutes, the methanol then being eliminated by distillation in vacuo on a water bath at 60°C; 117 grams of a beige yellow product are obtained which are used directly in the condensation reaction.

60 100 grams (0.40 mol) of 2-phenyl-2-dimethylamino-1-chlorobutane hydrochloride (m.p. = 145–147°C) are dissolved in 500 ml of iced water. 500 ml of diethyl ether are added and the mixture is made alkaline when cold by a concentrated sodium hydroxide solution until a 65 pH value of 12 is obtained.

65

The ether phase is separated and the aqueous phase is re-extracted twice with ether. The combined ether phases are washed with water and then dried over  $\text{Na}_2\text{SO}_4$ . The ether is eliminated at 20°C by distillation in vacuo.

A slightly viscous, colourless to light-yellow liquid is obtained.

5 Weight = 82.2 grams, yield = 96%.

In a suitable reactor 39.4 grams (0.27 mol) of sodium 4-methoxy-phenolate are dissolved in 125 ml of hexamethylphosphorotriamide (HMPT).

57 grams (0.27 mol) of 2-phenyl-2-dimethylaminochlorobutane in solution in 57 ml of HMPT are added with stirring over 30 minutes and at ambient temperature.

10 The reaction mixture is subsequently heated for 4 hours to 70°C and left to stand overnight.

After precipitation in water and the conventional treatments 52.6 grams of a mixture of the two products are obtained.

By crystallisation of the residue in hexane the 2-[(4-methoxy)phenoxy]-2-phenyl-N,N-dimethyl-n-butylamine (22) is isolated.

15 Weight = 10.5 grams, yield = 13%, m.p. = 55-57°C.

Hydrochloride: m.p. = 163-164°C.

From the mother liquors of this first product 1-[(4-methoxy)phenoxy]-1-phenyl-N,N-dimethyl-n-propylamine (21) is isolated in the form of DL camphosulphonate.

Weight = 40.2 grams, yield = 28%, m.p. = 154-155°C.

20 As the following toxicological and pharmacological tests demonstrate, the amino-ether oxides according to the invention possess local and spasmolytic anaesthetic properties. Certain products also have a considerable analgesic activity. These various properties make the products according to the invention valuable pharmaceutical agents.

The acute toxicity of the products of the invention was determined on groups of 20 Swiss

25 OF1 mice weighing 22 to 24 grams by intravenous route. These toxicities are expressed as the LD<sub>50</sub> corresponding to the dose at which a 50% mortality of the treated animals is noted after 8 days of observation. The limits of confidence of these values were determined by the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther. 1949, pages 96 to 99) and are given in table III.

30 The local anaesthetic activity on contact is determined on the cornea of the rabbit according to a method derived from the technique of Regnier (Regnier J.R. Salle, P. Bull. Soc. Pharmacol. 1926 33, 91).

Male albino rabbits weighing 2 to 3 kg are used in groups of 5. The product solution to be tested is injected in a volume of 0.2 ml into the conjunctival sac. The cornea is then stimulated

35 by means of a hair 3, 6, 10, 15, 20, 25, 45 and 60 minutes after injection.

The average number of stimulations is calculated for each group and this number is compared with that obtained with a lidocaine hydrochloride solution of equal concentration. The local anaesthetic activity is thus expressed in relation to this reference product.

The activity of the products is thus compared with that of a known anaesthetic: lidocaine

40 (table IV).

#### *Isolated organs.*

The spasmolytic activity of the products was studied in vitro with regard to two distinct agonists, namely:

45 1: barium chloride whose contracting effects was demonstrated on the rat duodenum; 2. nicotine whose contracting effect was demonstrated on the guinea-pig ileum.

The organ fragments were kept alive in a tank containing a solution of Tyrode (37°C, pH 7.2, oxygenated by the mixture O<sub>2</sub>/CO<sub>2</sub>, 95%/5%).

50 The isotonic contractions were recorded graphically on a physiograph by means of a transducer. For each substance the effect-dose straight line is determined according to semi-logarithmic coordinates and the EC<sub>50</sub> is calculated graphically, that is the concentration of the substance necessary to reduce by 50% the amplitude of the contraction of convulsant agent. The values obtained are compared with those of spasmolytic agents selected as reference and are determined under the same experimental conditions, namely:

55 —papaverine hydrochloride for the convulsant effect of barium chloride; —hexamethonium dibromide for the convulsant effect of nicotine (table V).

The analgesic activity of the products was studied on male Sprague-Dawley rats in groups of 15 by a method derived from that of Randall and Selito (Arch. Int. Pharmacodyn., 1957 (III) page 409). This method consists in causing a painful inflammation in the paw of the rat by

60 injecting 0.1 ml of a 20% brewer's yeast solution, then applying a pressure to the inflammation and determining the value of the pressure at which a painful reaction of the animal appears.

The activity of the products was studied after 1 hour of administration by oral route at the rate of one dose of 100 mg/kg in comparison with untreated animals. In this test aspirin was chosen as reference substance.

65 The analgesic effect of the products is expressed by the percentage increase of the pressure

endured by the treated animals in relation to that endured by the untreated animals.

The results of the analgesic activity of the product tested are expressed in relation to the activity of aspirin administered by oral route at a dose of 100 mg/kg. The results obtained are collated in table VI.

5 The compounds of the invention show anti-spasmodic, anaesthetic and analgesic activities useful in therapy. 5

These compounds are useful for all the spasmodic states of the smooth musculature and for the painful syndromes which are associated therewith.

By way of non-limiting example they can be used in:

10 —*gastroenterology*, in oesophagitis, gastroduodenal ulcer, gastritis, biliary dyskinesia, hepatic colic, spasmodic colitis, gastrointestinal malfunction as well as for the treatment of nausea and vomiting; 10

—*urology*, in nephritic colics and pain of the urinary passages;

—*gynaecology*, in spasmodic dysmenorrhea and dynamic dystocia (spasms of the cervix);

15 —in *vascular disturbances*, to alleviate the cerebral and peripheral ischemia associated with arterial spasms. 15

In these indications the unit therapeutic dose of the products is between 10 and 200 mg, preferably between 20 and 100 mg of active ingredient for 100 to 2000 mg of excipient.

The daily therapeutic dose is between 10 mg and 2 grams, preferably between 50 and 500 mg. 20 20

The active ingredients of the present invention are administered by the various routes applicable to humans and in the therapeutic forms compatible with these routes.

These various forms prepared from active substances (bases or salts) are produced by methods known per se.

25 Mention may be made as examples of these preparations of tablets, coated pills, capsules, ovules, powders, solutions, suspensions, ointments, gels and suppositories. The "sustained release" forms of these preparations can likewise be used. 25

To illustrate in a non-limiting way the production of these preparations, the production of tablets and of injectable isotonic solutions containing the active ingredients of the invention are given below. 30 30

1)	Tablets	mg	
	Active substance according to Example 2	50.0	
	Lactose	26.5	
35	Mannitol	55.0	35
	Medicinal white sugar	11.0	
	Polyethylene glycol 6000	5.0	
	Magnesium stearate	2.0	
	Gelatine	0.5	
40	Corn starch	50.0	40
	Total	200.0	

The gelatine and medicinal white sugar are dissolved separately in water. The two solutions are mixed and the polyethylene glycol 6000 is added thereto. 45 45

The lactose and mannitol are mixed intimately and then the active substance of Example 2, corn starch and the solution obtained above are added in order.

The paste is dried, granulated and screened, while adding the magnesium stearate and corn starch.

50 The obtained product is homogenised and compressed at the rate of 200.0 mg per tablet. 50

2)	Injectable isotonic solution	mg	
	Active substance according to Example 3	10	
	Sodium chloride	9	
55	Distilled water (sufficient to make)	1 ml	55

The isotonic solution is distributed in ampoules of suitable volume which, after sealing, are sterilised by thermal means known per se or the solution is sterilised by filtration and distributed in ampoules which are then sealed. All these operations are effected under sterile atmosphere.

60 In the latter case, it is preferable to add to the formula described 1% of benzyl alcohol as bacteriostatic agent, that is 10 mg of this alcohol per ml of solution. 60

**TABLE III**  
*LD<sub>50</sub> of the products of the invention in mice by intravenous route*

5	Example No.	Salt	LD <sub>50</sub> mg/kg <sup>-1</sup>	Limits of confidence mg/kg <sup>-1</sup>	5
10	1	DL camphosulph	30	29 - 32	
	2	H. maleate	42	41 - 43	
	3	H. maleate	41.4	38.5- 44.5	10
	4	H. maleate	26.8	25.1- 28.6	
	5	hydrochloride	37	28 - 49	
	6	H. maleate	48.6	44.6- 55.3	
	7	hydrochloride	37	36 - 39	
15	8	hydrochloride	52.3	48.2- 55.8	15
	9	hydrochloride	39	37 - 41	
	10	hydrochloride	43	41 - 45	
	11	hydrochloride	46.7	42.2- 51.6	
20	12	hydrochloride	34	30 - 39	
	13	H. maleate	48.4	45.0- 52.2	20
	15	DL camphosulph	160.0	143.8-178.0	
	17	hydrochloride	51.6	45.8- 58.4	
	18	H. maleate	27.3	25.2- 29.6	
	19	hydrochloride	30.7	25 - 37	
25	21	DL camphosulph	140.4	131.4-150.0	25
	22	hydrochloride	59.6	55.5- 64.0	
	lidocaine	hydrochloride	31.5		

30 The LD<sub>50</sub> of papaverine hydrochloride and of hexamethonium bromide are respectively 33.1 and 21.0 mg/kg. 30

**TABLE IV**  
*Results of the local anaesthetic activity of the products of the invention*  
35 (activity in 1% solution compared with that of lidocaine hydrochloride at an identical concentration) 35

	Example No.	Salt	Effect compared with lidocaine	
40	1	DL camphosulph	1.6	40
	2	H. maleate	2.2	
	3	H. maleate	1.4	
	7	hydrochloride	1.1	
45	9	hydrochloride	0.7	45
	11	hydrochloride	1.0	
	13	H. maleate	1.1	
	19	hydrochloride	0.95	
	12	hydrochloride	1.7	
50	21	DL camphosulph	0.45	50

The other compounds of the invention show a comparable local activity.

TABLE V

*Spasmolytic activity of the products of the invention compared with*  
 a) papaverine hydrochloride in the test with  $\text{BaCl}_2$   
 b) hexamethonium dibromide in the nicotine test.

Example No.	Salt	Rat duodenum	Guinea-pig ileum	5
		$\text{Ba Cl}_2$ 50 mg/l	nicotine 1 mg/l	
10				10
1	DL camphosulph	2.7	0.9	
2	H. maleate	5.4	1.2	
3	H. maleate	0.9	3.4	
5	hydrochloride	0.5	2.2	
15	hydrochloride	1.7	1.0	15
7	hydrochloride	0.4	1.4	
9	hydrochloride	0.4	1.7	
10	hydrochloride	1.9	2.6	
11	hydrochloride	1.2	2.3	
20	21	DL camphosulph	1.7	20
papaverine	hydrochloride	1	—	
hexa-				
methonium	dibromide	—	1	

25 The other compounds according to the invention have comparable spasmolytic properties. 25

TABLE VI  
 Results of the analgesic activity of the products of the invention at a dose of 100 mg/kg by oral 30 route in relation to aspirin 30

Example No.	Salt	Activities	
35	1	DL camphosulph	1
5	hydrochloride	2.5	35
10	hydrochloride	1.8	
11	hydrochloride	2.3	
aspirin		1	

40 *Index of activity of the products of the invention* 40

An index of activity relating to the products of the invention in relation to the reference substance used in each test was calculated for the local anaesthesia test and the spasmolysis tests in vitro.

45 This index I was calculated with regard to both the activity and the relative toxicity of the products of the invention in relation to the reference substances, namely lidocain hydrochloride, paraverine hydrochloride and hexamethonium dibromide. To eliminate the differences due to the molecular weights of the products, the calculations were made in mmoles. 45

50  $\text{EC}_{50}$  mmoles of the product studied. 50

$\text{EC}_{50}$  mmoles of the reference product

I =

55  $\text{LD}_{50}$  mmoles of the product studied 55

$\text{LD}_{50}$  mmoles of the reference product

60 For the products of the invention the results are collated in the following table VII. 60

TABLE VII

Relative indices of activity of the products of the invention in relation to:

—lidocaine hydrochloride for local anaesthetic activity;  
 5 —papaverine hydrochloride for spasmolytic activity in vitro on the rat duodenum;  
 —hexamethonium dibromide for spasmolytic activity in vitro on the guinea-pig ileum.

Example No.	local anaesthesia/ lidocaine hydro- chloride index	spasmolytic index/papaverine hydrochloride	spasmolytic index/hexameth- onium dibromide	
10				10
1	1.52	2.45	1.29	
2	2.95	6.90	2.42	
3	1.85	1.125	6.69	
15	5	0.56	3.85	15
7	1.30	1.89	1.75	
9	0.875	0.475	2.62	
10	—	0.525	3.50	
11	1.49	2.69	5.76	
20	12	1.84	4.09	20
13	1.71	—	—	
19	0.92	—	—	
21	2.00	7.28	11.33	

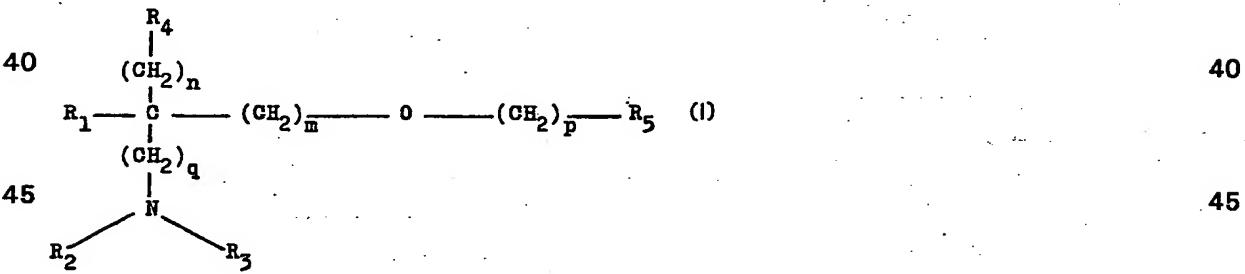
25 It is noted that the relative index of activity of the products of the invention in local anaesthesia is at least comparable to that of lidocaine hydrochloride and is in many cases 1.5 to 3 times higher.

30 The spasmolytic activity in vitro as compared with papaverine shows that, apart from the products of Examples 5, 9 and 10, the indices are up to seven times higher than those of the reference for the products of Examples 2 and 21.

Compared with hexamethonium dibromide, the indices are all nearly 7 to 11 times higher in respect of this reference for the products of Examples 3 and 21.

35 CLAIMS 35

1. Amino-ether oxides of formula:



50 in which:

R<sub>1</sub> is lower alkyl,

R<sub>2</sub> and R<sub>3</sub> which are the same or different are hydrogen or lower alkyl,

R<sub>4</sub> is a phenyl or phenoxy nucleus optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen or lower alkoxy,

55 R<sub>5</sub> is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical,

n is equal to zero, 1 or 2,

m and q are equal to 0 or 1,

60 p is an integer from 0 to 9 and their acid addition salts.

2. Amino-ether oxides according to claim 1, characterised in that the halogen atoms which appear therein are chlorine atoms or bromine atoms.

3. Amino-ether oxides according to claim 1 or 2, characterised in that R<sub>5</sub> is methyl.

65 4. Amino-ether oxide according to claim 1, which is 1-[(3,4-dimethoxy)benzyloxymethyl]-1- 65

phenyl-N,N-dimethyl-n-propylamine.

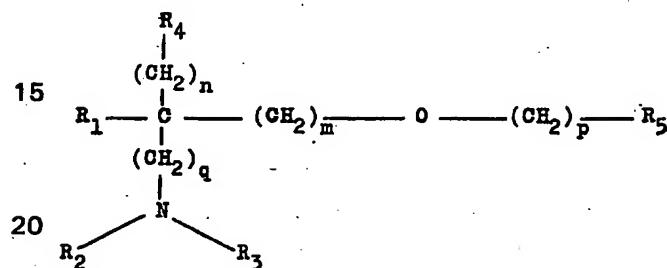
5. Amino-ether oxide according to claim 1, which of 1-[(3,4,5-trimethoxy)benzyloxy]-1-phenyl-N,N-dimethyl-n-propylamine.

6. Amino-ether oxide according to claim 1, which is 1-benzyloxymethyl-1-phenyl-N,N-dimethyl-n-propylamine.

5 7. Amino-ether oxide according to claim 1, which is 1-[(3,4,5-trimethoxy)benzyloxymethyl]-1-phenyl-N-methyl-n-propylamine.

8. Amino-ether oxide according to claim 1, which is 1-[(4-chloro)benzyloxymethyl]-1-methyl-1-[(4-methoxy)-phenyl]-N,N-dimethylamine.

10 9. Process for the preparation of amino-ether oxides of formula:



in which:

25 25 R1 is lower alkyl,

R2 and R3 which are the same or different are hydrogen or lower alkyl,

R4 is a phenyl or phenoxy nucleus optionally monosubstituted or trisubstituted by substituents which are the same or different, halogen or lower alkoxy,

30 R5 is a phenyl radical optionally monosubstituted to trisubstituted by substituents which are the same or different, halogen, lower alkyl, lower alkoxy or nitro, a pyridyl radical or a lower alkyl radical,

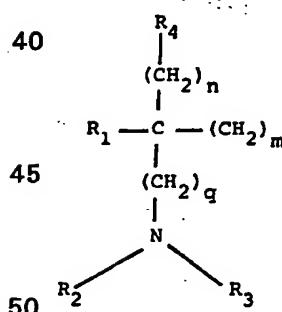
n is equal to zero, 1 or 2,

m and q are, independently of one another, equal to zero or 1,

p is an integer from 0 to 9,

35 and their acid addition salts,

characterised in that it consists in condensing a compound of formula AX with an alcoholate of formula BOM, one of A and B being the radical:



when the other is the radical R5-(CH2)p-, X being an anion and M being an alkali metal.

10. Pharmaceutical agent having in particular antispasmodic, anaesthetic and analgesic activities, characterised in that it contains an amino-ether oxide according to one of claims 1 to 8.

55 11. Compounds according to claim 1 as illustrated in any one of Examples 1 to 22 and their acid addition salts.